IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: **Chapman and King** Confirmation No.: **3379**

Serial No.: **09/719,045** Art Unit: **1644**

Filed: **December 7, 2000** Examiner: **David A. Saunders**

Title: DIVALENT ANTIBODY FRAGMENTS Customer No.: **34133**

VIA EFS Web
Filed: July 3, 2007

MAIL STOP APPEAL BRIEF- PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

REPLY BRIEF UNDER 37 CFR § 41.41

This Reply Brief is being filed in reply to the Examiner's Answer dated as mailed May 17, 2007. As it is being filed before July 17, 2007, it is timely

Preliminarily, Appellants appreciate the Office's clarification that the status of amendments is in reference to amendments filed after final rejection, none of which were filed in the present application.

Appellants, however, disagree with the allegation that the summary of claimed subject matter is deficient. The Office alleges that the summary uses terminology that differs from that of claim 1, and that the summary does not refer to all of the limitations of independent claim 1. The Office is directed to the summary chart of claim 1 included on page 4 of the Appeal Brief. The summary chart is duplicated below for the Office's convenience.

1. A divalent antibody fragment comprising two antibody heavy chains and at least one polymer molecule effective for increasing the circulating half-life of said fragment in covalent linkage,	page 3, lines 25-27 and page 2, lines 1-14
each heavy chain being covalently linked to the other by at least one non-disulphide interchain bridge linking the sulphur atom of a cysteine residue in one chain to the sulphur atom of a cysteine residue in the other chain,	page 3, lines 27-30
said cysteine residues being located outside of the variable region domain of each chain,	page 3, lines 30-31
characterised in that the at least one non-disulphide interchain bridge contains the at least one covalently linked polymer molecule.	page 3, lines 31-33

Support in the specification for the limitations of claim 1 was shown.

In responding to Appellants' arguments regarding the rejections of claims 1-10, 12-13, and 15, under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over, Gonzalez et al, the Office continues to miss an important distinction – Gonzalez et al does not disclose or suggest a divalent antibody fragment having a polymer molecule covalently linked to a cysteine residue outside of the variable domain on **EACH** heavy chain. Appellants do not challenge that Gonzalez et al describes monovalent antibody fragments having

a polymer molecule so linked. Appellants challenge the Office's assumption that, because Gonzalez et al describes monovalent antibody fragments so linked, and describes divalent antibody fragments linked together by a polymer molecule to form a dumbbell-shaped structure, albeit with no discussion of where the polymer is linked to the antibody fragment(s), Appellants' invention is disclosed. It is not.

Before addressing the Office's arguments in detail, Appellants note that the Office mischaracterized the Appellants' arguments regarding attachment as relating to attachment to the polymer. This mischaracterization was based upon the repeated error by the Office in assuming that the discussion that Fab' fragments are attached via a hinge region cysteine to the polymer is a disclosure that the dumbbell-shaped structures are also attached through a hinge region cysteine. It is not. The Office is erroneously reading this disclosure into the reference. Regardless, Appellants were clearly referring to where the polymer is attached to the **fragments**, as this is what is specified in the claims, not where the fragments are attached to the polymer.

The Office argues that the claims include attaching two Fab' fragments via a cysteine residue outside the variable region on **each** heavy chain. As acknowledged by the Office, however, the reference does not disclose such fragments.

> It is the examiner's position that **the disclosure of Gonzalez need not ipsis verbis disclose** that, when a polymer molecule used to link together two antibody fragments to form a dumbbell-shaped structure, such linkage to each of the two antibody fragments is to be formed by the type of coupling chemistry shown at col. 120, line 15-col. 122, line 31. The disclosure is anticipating for this structure, because it is reasonably considered to disclose all

> combinations that can result by choosing one the possible kinds of conjugate constructs . . . taught and then choosing one of **numerous** kinds of coupling/linking chemistry taught. **The examiner finds no need** for Gonzalez et al to have specifically pointed to a particular one of the combinations, since they are all within the scope of what the reference teaches.

(Examiner's Answer, page 10, emphasis added.) The standard for anticipation is not that the combination is "within the scope of what the reference teaches." Notably, the Office cites no case law in support of this position.

Further, the Office's assertions are inconsistent with the case law regarding inherency. The case law regarding inherency was cited previously, but is reiterated here. To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference…Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing **may** result from a given set of circumstances is not sufficient." MPEP 2112, IV, citing *In re Robertson*, 169 F.3d 743, 745, 49 U.S.P.Q.2d 1949, 1950-51 (Fed. Cir. 1999), emphasis added. The Office continues to argue probabilities and/or possibilities, which are inappropriate for inherency.

> It is reasonable to take the position that one who is considering what Gonzalez et al anticipate would have arrived at the instant invention by listing of all of the **possibilities** that can result when one chooses from among the various kinds of conjugate constructs . . .

(Examiner's Answer, page 10.) The Office's argument is not unlike the famed argument that a group of monkeys typing on a typewriter would eventually type a Shakespearean play. That may be true, but it is not the standard for anticipation.

Finally, to the extent the Office is relying upon the disclosure of the genus, i.e., the dumbbell-shaped structure in general, as disclosing the claimed species, the case law regarding anticipation of a species is unavailing. For a genus to anticipate a species,

> [o]ne of ordinary skill in the art must be able to draw the structural formula or write the name of each of the compounds included in the generic formula before any of the compounds can be "at once envisaged." One may look to the preferred embodiments to determine which compounds can be anticipated.

In re Petering, 301 F.2d 676, 133 USPQ 275 (CCPA 1962). Considering the number of potential cross-linking sites on the antibody fragments contemplated, i.e., N-terminal amino groups and epsilon amino groups on lysine residues, the amino, imino, carboxyl, sulfhydryl, hydroxyl, or other hydrophilic groups (see col. 41, line 63, through col. 42, line 23 of Gonzalez et al.) and the number of amino acids containing such sites per antibody fragment, and that the dumbbell structure could comprise divalent antibody fragments on each end, Appellants submit that one of ordinary skill could not at once envisage Appellants' invention from the description of Gonzalez et al., particularly considering the discussion regarding $(Fab')_2$ fragments, unless one had Appellant s' disclosure.

Nor does Gonzalez et al render Appellants' invention obvious. As Appellants have repeatedly emphasized, when Gonzalez et al specifically discusses divalent antibody fragments, it specifies that the cyteine residue in the hinge region of one of the chains be changed to a

different amino acid so that a linkage **as claimed** does **not** occur. The Office cannot continue to dismiss this disclosure, which is contrary to its assumptions, as obfuscations or confusion, or as not having been relied upon by the Office. A reference must be considered in its entirety. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). The Office does not get to pick and choose which portions it will rely upon. When considered in its entirety, Gonzalez et al clearly teaches away from having the polymer replace the disulfide bridge between antibody fragments. Gonzalez et al, thus, teaches away from Appellants' invention.

Regarding the rejection of claims 13-14 for obviousness over Gonzalez et al in view of Barbanti et al, the Office surprisingly makes the conclusory statement that only a person having less than ordinary skill in the art would not have been motivated to extend the half-life of an antibody that is being administered for the purpose of neutralizing an inflammatory molecule such as TNF-alpha. First, the analysis for obviousness cannot based upon conclusory statements as advanced by the Office; the analysis for obviousness must be based upon articulating reasoning with a rational basis for combining. *See KSR International Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007). Second, as argued previously, Barbanti et al does not overcome the deficiencies of Gonzalez et al. Barbanti et al does not disclose or suggest a divalent antibody fragment as claimed. Accordingly, even if there were a motivation to combine, a combination of the references would not result in Appellants' invention.

CONCLUSION

Claims 1-10 and 12-15 are not anticipated by, or obvious over, the art cited by the Office.

Appellants request that all rejections be withdrawn and that all claims be allowed.

Respectfully submitted,

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/Doreen Yatko Trujillo/
Registration No. 35,719

COZEN O CONNOR P.C.
1900 Market Street, 7th Floor
Philadelphia, PA 19103-3508
(215) 665-5593 - Telephone
(215) 701-2005 - Facsimile